# Medical Science

# Nephroprotective mechanisms, therapeutic potential and perspective on melatonin use for drug-induced nephropathy

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## ABSTRACT

The research aimed to review the effects and mechanisms of action of the pineal hormone melatonin, to study the nephroprotective effect of exogenous melatonin in conditions of drug-induced nephropathy, and to assess the prospects of its use for prevention and treatment of kidney diseases based on the literature data and results of own studies. According to literature and results of our previous research, the nephroprotective effect of melatonin has been shown in various experimental models of acute renal injury (AKI). Numerous studies established the antioxidant, anti-inflammatory, anti-apoptotic, immunomodulatory, and cytoprotective effects of melatonin, and showed its ability to restore the function and structure of the kidneys. The objective of the current study was to evaluate the effects of melatonin (5 mg/kg) on the animal model of acetaminophen-induced AKI. The obtained results show the ability of melatonin to reduce the severity of damage and prevent kidney dysfunction associated with acetaminophen over dose. Treatment with melatonin was suppressed the progression of oxidative stress in kidney tissue through the limitation of lipid and protein peroxidation and activation of the key antioxidant enzymes. Results of research complement to existing data on the nephroprotective activity of melatonin and substantiate the high therapeutic potential and prospects of melatonin use as adjunctive therapy of drug-induced nephropathy.

**Keywords:** drug-induced nephropathy, melatonin, nephrotoxicity, nephroprotection

## 1. INTRODUCTION

Pineal hormone melatonin (N-acetyl-5-methoxy tryptamine) has a variety of biological effects and is considered the main regulator of circadian rhythms and neuroendocrine functions. Melatonin (N-acetyl-5-methoxytryptamine) was discovered and isolated from

the pineal gland in 1958 (Lerner, 1958). According to Eghbal et al. (2016), Reiter et al. (2010) and Tordjman et al. (2017), melatonin is mainly secreted by the pineal gland, cerebellum, retina, bone marrow cells, platelets, lymphocytes, and enterochromaffin cells of the gastrointestinal tract. As noted by Ekmekcioglu (2006), melatonin receptors are found in both central and most peripheral organs and tissues. Melatonin (MT) receptors were identified in the kidneys more than 20 years ago and localize on the basolateral membranes of the convoluted tubules (Slominski et al., 2013; Song et al., 1997). Since its identification, melatonin has been well studied for its roles in complex physiological and pathological processes from controlling circadian rhythm to cancer proliferation (Raza and Naureen, 2020). Thus, in addition to regulating sleep-wake rhythms and seasonal adaptation, melatonin modulates numerous neuronal, endocrine, and immune functions (Eghbal et al., 2016).

Tordjman et al. (2017) emphasizes that melatonin synchronization of peripheral oscillators creates the possibility of individual adaptation to periodic changes in the internal and external environment. According to Pandi-Perumal et al. (2007), Eghbal et al. (2016) and Emet et al. (2016), a decrease in endogenous melatonin formation and expression of MT-receptors is observed in aging and a wide range of pathological conditions: sleep disorders, stress, pain, endocrine and metabolic disorders (including type II diabetes), mental and neurodegenerative disorders, cancer, and cardiovascular diseases.

As stated by Reiter et al. (2017) and Galano et al. (2018), melatonin, due to its direct anti-radical activity and ability to potentiate the antioxidant system, is a very important antioxidant. Numerous researchers (Bonnefont-Rousselot and Collin, 2010; Reiter et al., 2017; Sanchez-Barcelo et al., 2010; Sharman and Bondy, 2016) report a therapeutic effect of melatonin in various pathologies associated with oxidative stress. In addition, the results of many experimental studies (Majidinia et al., 2017; Pacini et al., 2016; Reiter et al., 2018; Tordjman et al., 2017) indicate immunostimulatory, anti-inflammatory, anti-apoptotic, cytoprotective, oncostatic and anti-aging effects of melatonin. Moreover, in the opinion of Andersen et al. (2015) and Sharman and Bondy (2016), the benefits of melatonin are its natural origin, wide availability and relative safety, making melatonin a potential therapeutic agent. The efficacy and safety of melatonin have been extensively investigated in multiple laboratory studies and several clinical trials, which verified its potential therapeutic usefulness in a variety of pathologies (Sanchez-Barcelo et al., 2010; Raza and Naureen, 2020).

According to literature and results of own research, the nephroprotective effect of melatonin has been shown in various experimental models of ischemia-reperfusion and toxic acute renal injury: cisplatin-induced (Dudka et al., 2018; Kilic et al., 2013), gentamicin-induced (Casanova et al., 2017; Lee et al., 2012; Shchudrova et al., 2019), rhabdomyolysis-induced (Tsai et al., 2017; Yang et al., 2016; Zamorskii et al., 2019), and others. The studies established the mechanisms of nephroprotective action of melatonin – antioxidant, anti-inflammatory, anti-apoptotic, and showed its ability to restore the function and structure of the kidneys of rats. Melatonin is also considered as a promising agent for the pathogenetic correction of diabetic nephropathy and chronic kidney disease progression (Hrenak et al., 2015; Ohashi et al., 2019; Quiroz et al., 2008; Russcher et al., 2012).

Acetaminophen (paracetamol) is one of the most widely used analgesic and antipyretic. However, acetaminophen overdose is among the most common causes of both intentional and unintentional drug poisoning. Acetaminophen poisoning is associated with the hepatotoxicity and/or nephrotoxicity with development of acute kidney injury (AKI) in 2-10% of cases (Stollings et al., 2016). Thus, the objective of the research was to study the nephroprotective effect of melatonin on the animal model of acetaminophen-induced AKI.

## 2. MATERIAL AND METHODS

The experiments were conducted in March 2019 on nonlinear mature white rats weighing 150-200 g, maintained in the vivarium conditions and randomly distributed into three groups (n=7). Group I – control; group II – acetaminophen-induced AKI; group III – administration of melatonin (Sigma-Aldrich, USA) at a dose of 5 mg/kg against the background of AKI development. Doses of drugs were determined in accordance with the literature and the results of our previous research (Dudka et al., 2018; Shchudrova et al., 2019; Zamorskii et al., 2019). Acetaminophen-induced AKI was caused by a single intraperitoneal administration of acetaminophen (paracetamol, Health, Ukraine) at a dose of 750 mg/kg (Singh et al., 2012). Melatonin was administered 1 h after paracetamol injection. Animals were withdrawn from the experiment 24 h later, while blood, urine and kidneys were sampled for biochemical and histopathological assessments.

Kidney function was evaluated by diuresis, plasma creatinine level, creatinine clearance, urine protein excretion, fractional excretion and reabsorption of sodium, plasma potassium level, and urine pH. Plasma and urine creatinine levels were determined using the Jaffe reaction; urine protein content – using the sulfosalicylic acid precipitation test; sodium and potassium levels – using an electronic flame photometry method.In kidney tissue homogenates  levels of malondialdehyde (MDA) and protein oxidative modification products (OMP), catalase and glutathione peroxidase (GPx) activity was determined (Kamyshnikov, 2016).

Statistical processing of the obtained data was performed using the SPSS Statistics 17.0 software. All data are represented as a mean ± standard error of the mean (M±m). Estimation of the differences between the samples was conducted using a parametric Student's t-test and a nonparametric Mann-Whitney U test. P<0.05 was accepted as statistically significant.

All studies were carried out in accordance with the criteria outlined in the European Union Directive 2010/63/EU "On the protection of animals used for scientific purposes" (2010). The study was approved by the Biomedical Ethics Committee of the Higher State Educational Establishment of Ukraine "Bukovinian State Medical University" (experimental study; ethical approval number N3/2018).

## 3. RESULTS

In our experiment, a single administration of the toxic acetaminophen dose to rats (group II) resulted in drug excessive accumulation and damage to the proximal tubular cells. It is known, that cellular toxicity of acetaminophen is associated with translocation and dysfunction of Na+-K+-ATPase, which ensures effective sodium reabsorption. In rats with acetaminophen-induced AKI a decrease in sodium reabsorption and, accordingly, an increase in fractional sodium excretion was found (Table 1). An increase in the sodium concentration in the tubular fluid led to the activation of tubuloglomerular feedback with a 2-fold decrease in glomerular filtration rate (GFR), reduced urine output, and development of retention azotemia. Significant proteinuria compared to the control confirms the severe toxic damage to renal tubular cells. In animals that received melatonin treatment (group III) renal dysfunction was less pronounced. Melatonin counteracted the nephrotoxic effect of acetaminophen, as evidenced by the prevention of significant sodium loss due to maintenance of the reabsorption capacity of tubular cells, restoration of urine output due to maintenance of GFR, and prevention of retention azotemia and significant proteinuria.

**Table 1** Influence of melatonin (5 mg/kg) on kidney function of rats with acetaminophen-induced AKI

| Index | Control | Acetaminophen-induced AKI | Acetaminophen + Melatonin |
|---|---|---|---|
| Urine output, ml/100 g/2 h | 5.52±0.19 | 3.40±0.15* | 4.43±0.10# |
| Plasma creatinine, μmol/L | 67.47±4.74 | 115.81±6.30* | 82.94±5.38# |
| Glomerular filtration rate, μl/min | 399,7±32,5 | 198.9±17.0* | 313.8±19.2# |
| Urine protein excretion, mg/2 h | 0.015±0.002 | 0.093±0.017* | 0.032±0.004# |
| Fractional sodium excretion, % | 1.05±0.14 | 3.51±0.25* | 1.51±0.18# |
| Sodium reabsorption, % | 96.81±0.24 | 93.88±0.37* | 95.88±0.32# |
| Plasma potassium, mmol/L | 5.75±0.33 | 5.14±0.15 | 5.57±0.25 |
| Urine pH | 7.74±0.07 | 7.21±0.08* | 7.44±0.04# |

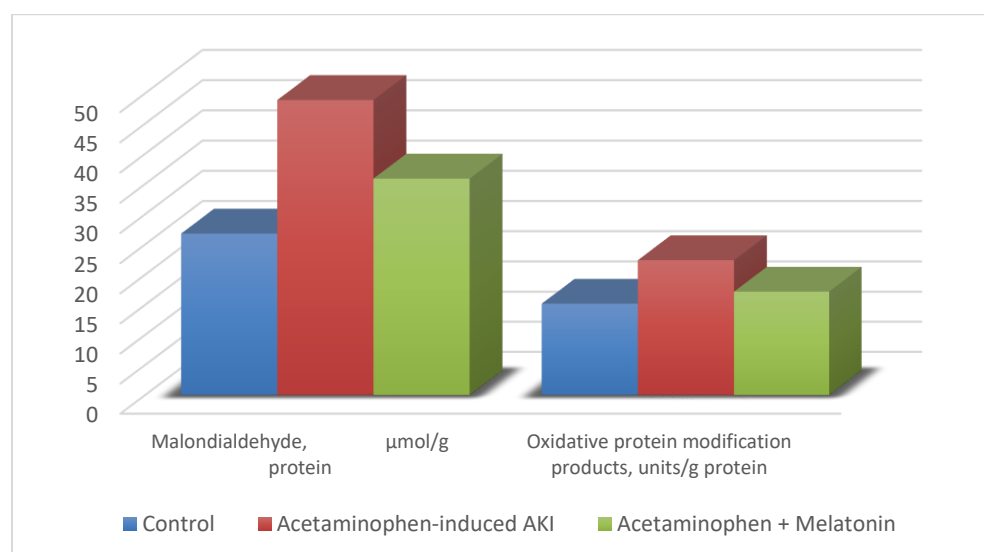*p<0.05 versus control; #p<0.05 versus acetaminophen-induced AKI



**Figure 1** Influence of melatonin (5 mg/kg) on the peroxidation processes in kidney tissue of rats with acetaminophen-induced AKI

Figure 1 and 2 shows the state of the prooxidant-antioxidant balance in the kidney tissue of experimental animals. Acetaminophen overdose induced the oxidative stress from the intensification of ROS production, lipid and protein peroxidation processes and the simultaneous decline of the enzymatic antioxidant capacity. In animals from group II (acetaminophen-induced AKI), a significant increase in the level of lipid peroxidation end-product malondialdehyde (MDA) and protein oxidative modification products (OMP) was found in kidney tissue ($p < 0.05$ compared to the control group). Acetaminophen also compromised local antioxidant system, manifested in a decrease in glutathione peroxidase (GPx) and catalase (CAT) activity ($p < 0.05$ compared to the control group). Melatonin showed a significant antioxidant effect manifested in attenuation of both lipid and protein peroxidation in the kidney tissue, along with an increase in the GPx and CAT activity compared to untreated animals ($p < 0.05$).
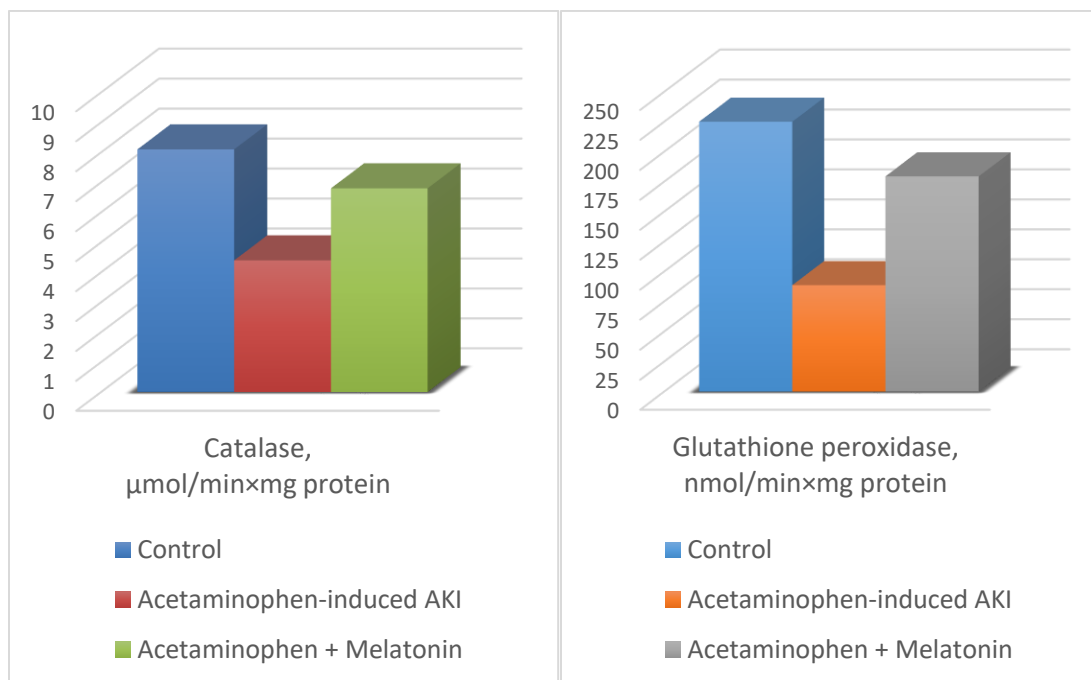


**Figure 2** Influence of melatonin (5 mg/kg) onthe activity of antioxidant enzymes in kidney tissue of rats with acetaminophen-induced AKI

## 4. DISCUSSION

To date, various molecular mechanisms of action of melatonin are known (Eghbal et al., 2016; Majidinia et al., 2017; Reiter et al., 2010; Tordjman et al., 2017). Melatonin affects cell physiology through the membrane and nuclear receptors, as well as directly interacts with cytosolic molecules. Besides, melatonin has receptor-independent effects due to its direct antiradical activity. The receptor signalling mechanism is the activation of three types of membrane-specific receptors Mel1a (MT1) and Mel1b (MT2), MT3, and the nuclear receptor RZR/RORα (Emet et al., 2016; Li et al., 2013). MT1 receptors are common in the anterior pituitary gland (causes suppression of prolactin secretion) and SCN of the hypothalamus (anatomical area of the circadian clock), as well as in the cortex, thalamus, basal ganglia, hippocampus, cerebellum, blood vessels, liver, kidneys, pancreas, and immune system. MT2 receptors are found in the retina, hippocampus, cortex, paraventricular nucleus, cerebellum, blood vessels, liver, kidneys, gastrointestinal tract, muscles, and adipose tissue. The receptor-mediated mechanism is a complex process, and varies depending on the type of cells and tissues. Through the binding to membrane receptor (MT1/MT2/MT3), melatonin activates various cascades of secondary messengers (Pandi-Perumal et al., 2008). Activation of Gi-coupled MT1 receptors results in inhibition of adenylate cyclase with decreased cAMP production and modulation of protein kinase A activity. Activated MT1 receptors also inhibit the phosphorylation of transcription factor CREB (cAMP response element-binding protein) and the formation of c-*fos* and jun B. Stimulation of the Gq-coupled subtype MT1 receptors leads to the activation of C-β phospholipase corresponding to increase in intracellular levels of inositol triphosphate and calcium, and activation of the signalling pathways of calmodulin and calreticulin. Activation of MT1 receptors also enhances potassium transmembrane current by activating the internal potassium channel rectifier Kir3 (GIRK), and potentiates prostaglandin F2α and ATP-mediated activation of protein kinase C. Stimulation of MT2 receptors further reduces the formation of cGMP in target cells. The melatonin MT3 receptor is the enzyme quinone reductase type 2 (NQO2), which is expressed in different areas of the brain, and its activation leads to the hydrolysis of phosphoinosites. Activation of nuclear

RORα receptors causes the immunomodulatory and anti-inflammatory effects of melatonin, as well as the activation of antioxidant enzymes (Emet et al., 2016; Reiter et al., 2010).

Melatonin exerts its antioxidant action through both receptor-mediated and receptor-independent pathways. The receptor-mediated activity of melatonin is attributed to its ability to increase the activation and expression of a variety of antioxidant enzymes. Moreover, melatonin also decreases the enzymatic activity of nitric oxide synthetase (NOS) and NO-mediated production of more potent oxidant peroxynitrite species (ONOO−). Therefore, melatonin mediates the multifaceted stimulation of antioxidant enzymes and enhances cellular protection against oxidative stress (Raza and Naureen, 2020). The receptor-independent mechanism of action of melatonin is the ability of direct free radical scavenging (Ding et al., 2014; Hardeland, 2009; Reiter et al., 2017, 2018). Melatonin protects lipids, proteins and nuclear DNA from oxidative damage by donating free electrons and inactivating the most toxic oxidative reactive agents: hydroxide radical (•OH), peroxynitrite anion (ONOO), singlet oxygen ($^1O_2$), superoxide anion radical $O_2(−)$, hydrogen peroxide ($H_2O_2$), nitric oxide (NO•) and hypochlorous acid (HClO). According to Slominski et al. (2012) and Reiter et al. (2017, 2018), melatonin due to its amphiphilic properties, easily enters the cell nucleus and mitochondria, where it captures free radicals of oxygen and nitrogen, directly inhibits the mitochondrial permeability transition pore (MPTP), reduces cytochrome c release, and improves oxidative phosphorylation processes in the mitochondrial respiratory chain. It was found (Reiter et al., 2017; Majidinia et al., 2017) that metabolites of melatonin (3-hydroxymelatonin, etc.) are also powerful scavengers of free radicals, enabling the functioning of the "antioxidant cascade of melatonin". Inhibition of peroxynitrite formation and blockade of transcription factors NFk-B, HIF, Nrf2, which cause the formation of pro-inflammatory cytokines results in the anti-inflammatory effect of melatonin (Eghbal et al., 2016). The antiapoptotic effect of melatonin is associated with antiradical protection of mitochondria and inhibition of the internal pathway of apoptosis (Reiter et al., 2017, 2018).

In addition to direct antiradical action, melatonin stimulates the synthesis and activation of antioxidant enzymes – catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GRd). An increased CAT and SOD activity is associated with the enhanced metabolism of H2O2 into water and oxygen instead of its conversion into potent free radicals (Raza and Naureen, 2020). GPx supplements the antioxidant action and catalyzes the reduction of $H_2O_2$ by reduced glutathione (GSH) into H2O and oxidized form glutathione disulphide (GSSG). Glutathione reductase, which activity is also stimulated by melatonin, reduces GSSG into GSH, thereby recovering the glutathione in the process of $H_2O_2$ metabolism. Thus, GSH plays critical role in protecting cells from oxidative damage and the toxicity of xenobiotics.

Oxidative stress is a key mechanism of the acetaminophen-induced hepato- and nephrotoxicity. The administration of acetaminophen at toxic doses leads to the excessive formation of the highly reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI), which is inactivated by binding to GSH. When glutathione stores are depleted, NAPQI binds to SH-groups of cellular proteins, leading to mitochondrial dysfunction and impairment of energy metabolism, development of oxidative stress, induction of apoptosis, and ultimately necrotic cell death with the subsequent liver and/or kidney malfunction (Pazhayattil and Shirali, 2014; Stollings et al., 2016). The obtained experimental data are in line with several other research results (Ilbey et al., 2009; Sener et al., 2003) showing the ability of melatonin to reduce the severity of damage and prevent kidney dysfunction associated with acetaminophen overdose. The multifaceted effects of melatonin, in particular, direct ROS scavenging activity and ability to restore glutathione level, combined to anti-apoptotic, anti-inflammatory and cytoprotective effect appear to be the key mechanism of the nephroprotective action of melatonin in conditions of acetaminophen-induced AKI.

## 5. CONCLUSION

In conditions of acetaminophen-induced AKI nephroprotective effect of melatonin manifests by the preservation of the kidney function and restoration of the local prooxidant-antioxidant balance. Results of research complement to existing data on the nephroprotective activity of melatonin and substantiate the high therapeutic potential and prospects of melatonin use as adjunctive therapy of drug-induced nephropathy.

**Ethical approval**

The study was approved by the Biomedical Ethics Committee of the Higher State Educational Establishment of Ukraine "Bukovinian State Medical University" (experimental study; ethical approval number N3/2018).

**Data and materials availability**

All data associated with this study are present in the paper.

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